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Review article

A Perspective about coronavirus disease 2019 (COVID-19)

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The Author claims to have contributed similarly to the original idea, study design, data collection, data analysis, draft writing and article writing (GFC).

Abstract

COVID-19 is the acronym for coronavirus disease 2019, which is caused by SARS-CoV-2, that was isolated and genotyped from respiratory samples collected from patients in the city of Wuhan (China), after an outbreak of pneumonia of non-identified etiology on december 2019. Its arrival to Ecuador has highlighted the relevance of this microorganism, and its characteristics. Below, we propose a brief review of the literature in relation of this new pathogen and its disease, as well as key points for its control at health facilities.

Keywords: Communicable diseases; coronavirus; SARS Virus; COVID-19;

Abstrato

COVID-19 é o acrónimo para doença coronavírus 2019, que é causada pela SRA-CoV-2, que foi isolada e genotipada a partir de amostras respiratórias recolhidas de doentes na cidade de Wuhan (China), após um surto de pneumonia de etiologia não identificada em dezembro de 2019. A sua chegada ao Equador destacou a relevância deste microorganismo, e as suas características. A seguir, propomos uma breve revisão da literatura em relação a este novo patógeno e sua doença, bem como pontos-chave para seu controle nas unidades de saúde.

Palavras-chave: *Doenças Transmissíveis; coronavirus; vírus SARS; COVID-19*;

Introduction

Between late november and early december 2019, an epidemiological event of interest occurred in the city of Wuhan, Hubei province, in the People's Republic of China, where a series of reports of pneumonia of unknown origin appeared among its population. It was determined that the virus was a member of the coronavirus family, and was closely related to SARS-CoV, the etiological agent of the 2003 Severe Acute Respiratory Syndrome (SARS), initially called Wuhan virus, later renamed 2019-nCoV (2019 novel coronavirus).[1, 2]

The government of the People's Republic of China, through the Chinese Center for Disease Control, reported the outbreak to the WHO on January 3, 2020. As of 30 January 2020, the Director-General of WHO declared the

outbreak of a new strain of coronavirus as a public health emergency of international importance (the fifth time since 2005), with the purpose of preparing healthcare systems to take preventive and contingency measures, in the event of the possible global spread of the disease. On 11 March 2020, the WHO, through the Director-General, declared COVID-19 (coronavirus disease 2019) a pandemic.[3, 4, 5]

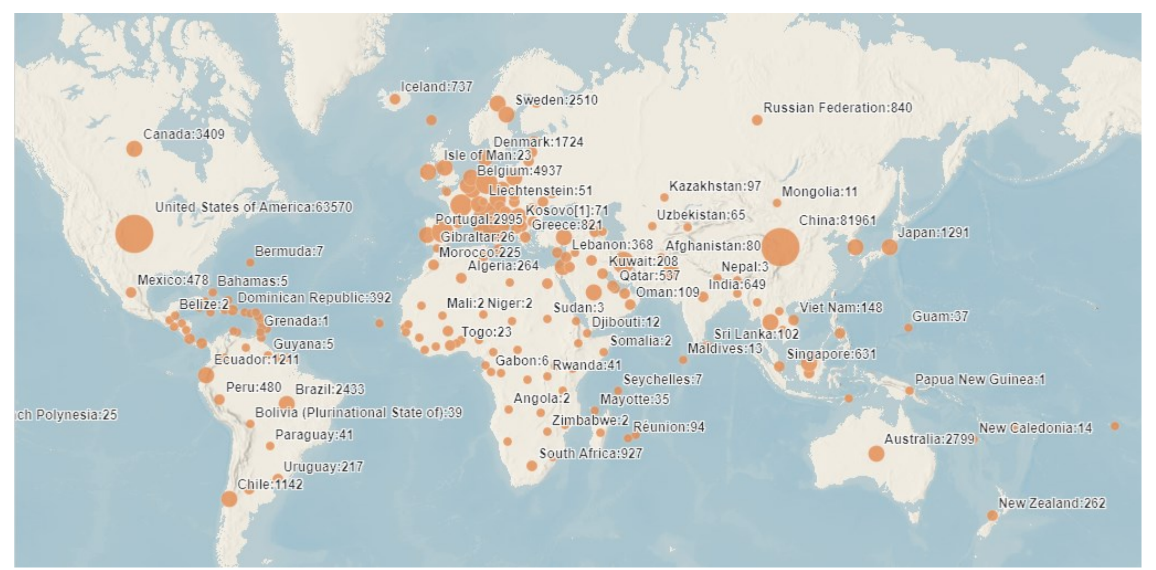


Figure 1. Map of distribution of COVID-19 cases.
Source: World Health Organization; available at: https://experience.arcgis.com/experience/685d0ace521648f8a5beeeee1b9125cd

The pandemic, on 19 March 2020, reported 242,191 confirmed cases, 84,962 recovered and 9,843 deaths worldwide.[6] Ecuador is still in general quarantine. On April 22, it reports 10,850 confirmed cases, 1,262 recovered and 537 confirmed deaths from COVID-19.[7]

Discussion

Virology aspects

Microbiologically, the Coronaviridae family are single-stranded enveloped RNA viruses (with two viral glycoproteins, S [richly glycosylated] and M [matrix transmembrane protein located inside the envelope]).[8]

Coronaviruses, which include OC43, NL63, hCoV-229E and HKU1, which most commonly affect humans, usually causes mild respiratory infections. Viral agents such as coronavirus of severe acute respiratory syndrome (SARS-CoV) and coronavirus of middle-eastern respiratory syndrome (MERS-CoV) often emerge as zoonotic infectious agents in humans through a series of mutations until they reach humans, which is what was presumed to have caused the 2019-nCoV infection.[9]

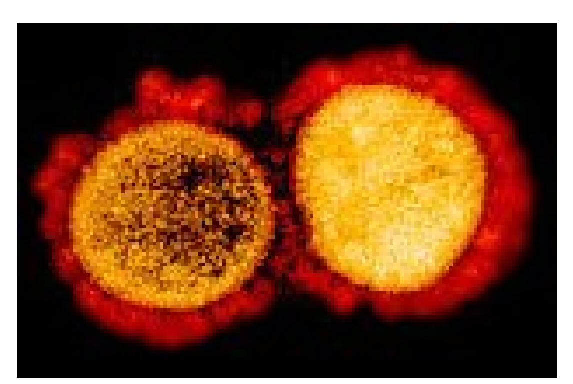


Figure 2. Novel coronavirus SARS-CoV-2
Particle transmission electron micrograph of SARS-CoV-2 virus isolated from a patient. Captured and enhanced color image at NIAID's Integrated Research Facility (IRF) in Fort Detrick, Maryland. Credit: NIAID. Available at: https://www.flickr.com /photos/niaid/49645402917/.

In 2002, SARS cases were reported in China's Guangdong province, which were disseminated by a physician who treated the patients during his stay in a Hong Kong hotel on 21 February 2003, who fell ill and died the next day. While in the hotel, he was able to transmit the virus to 10 other residents from Singapore, Vietnam, Canada, and the United States. It was this small group, in turn, that allowed the infection to spread to 8,000 other people in 29 countries. Ten years later, cases of severe pneumonia were reported in the Arabian Peninsula, with 50% of those infected dying10. In both cases, the etiological agents belonged from the Coronaviridae family, the first one was called SARS-CoV and the second one, MERS-CoV.[10]

Zhu et al. performed the isolation from bronchial-alveolar lavage samples from 7 patients in Beijing, from which nucleic acids were subsequently extracted, using cell culture media, performing impartial high throughput

sequencing (looking for viruses and bacteria, as the aetiology was unknown), and Real Time Reverse Transcription PCR (RT-PCR) assay for viral RNA, with the "objective of obtaining a RdRp region consensus of bread β-CoV". The extracted RNA was used as a template to clone and sequence the genome, obtaining 20,000 viral readings from single samples and showing more than 85% of identity with a CoV similar to a bat SARS (bat-SL-CoVZC45, MG772933.1).[11]

To further characterize the virus, de novo sequences of the 2019-nCoV genome were obtained from clinical samples and virus isolation from respiratory epithelial cells, obtaining two almost complete coronavirus sequences (BetaCoV/Wuhan/IVDC-HB-04/2020, BetaCoV/Wuhan/IVDC-HB-05/2020 | EPI_ISL_402121) and one complete sequence (BetaCoV/Wuhan/IVDC-HB-01/2020 | EPI_ISL_402119)[11], which had 89 % CoV nucleotide sequence identity (bat-SL-CoVZC45, MG772933.1), and were therefore grouped within the subgenus sarbecovirus, which has the typical organization of a betacoronavirus. In conclusion, the isolated viruses were different from MERS-CoV and SARS-CoV, the three coronaviruses [2019-nCoV Wuhan, together with 2 SARS-like strains derived from bats (ZC45 and ZXC21)] form a different clade and, therefore, it was determined that they constituted a new viral agent (2019-nCoV).[11]

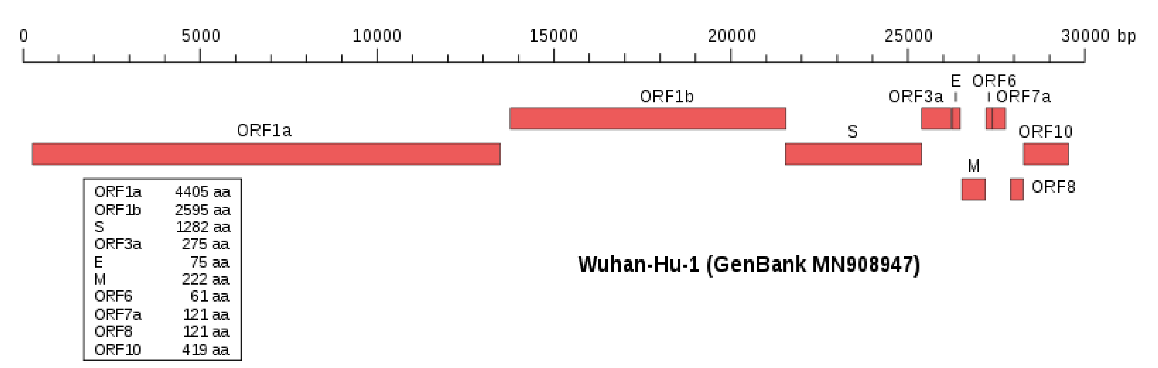


Figure 3. SARS-CoV-2 genome organization (Wuhan-Hu-1 isolation, GenBank Acc MN908947). Furfur. Wikimedia Commons, el repositorio de medios libres. Crédito: Furfur. Disponible en: https://commons.wikimedia.org/wiki/File:SARS-CoV-2_genome.svg. Licencia CC-ASA-4.0 internacional.

Yang et al. proposed that the angiotensin converting enzyme receptor could be key in 2019-nCoV infection, so that the virus would access the systemic circulation and infect other organs with this type of receptor, similar to the 2002-2003 SARS-CoV.[12]

Zhou et al. successfully isolated the virus (called 2019-nCoV BetaCoV/Wuhan/WIV04/2019) from Vero E6 and Huh7 cells in serum neutralization assays on Vero E6 cells, using all five patient sera that were positive for IgG. The researchers report that all samples were capable of neutralizing 100 DICT50 (50% tissue culture infectious dose) as well as cross neutralization with anti-SARS-CoV horse serum at 1:40 dilutions.[13]

Kim et al. in Korea isolated from nasopharyngeal and oropharyngeal samples by RNA amplification of the replicated virus cell culture medium and analysis of the NS sequence with a gene compared to 57 human coronaviruses (including Wuhan's), a beta coronavirus called BetaCoV/Korea/KCDC03/2020, which has been shown to have a homology of greater than 99.5 % to SARS-CoV-2.[13-14] Various authors [12-14] have determined that SARS-CoV and SARS-CoV-2 possess an interaction with the angiotensin-converting enzyme 2 receptor. Zhang et al. mention

Pangolin-CoV as the common ancestor of 2019-nCoV (genome similarity 91.02%) instead of Bat-CoV RaTG13 (genome similarity 90.55%), in addition to the fact that Pangolin-CoV protein S1 is related to 2019-nCoV more closely than RaTG13.[15]

Therefore, with evidence based on the taxonomy, the coronavirus study group (CSG) has formally classified it as a sister strain of SARS-CoV, and designated it as coronavirus 2 of the Severe Acute Respiratory Syndrome (SARS-CoV-2).[16]

On the basis of the microbiological investigation carried out, it was determined that respiratory tract fluid or tissue samples are the main source for determining the infectious agent by PCR (polymerase chain reaction) detection.[10-15]

Clinical manifestations

The criteria for identifying suspicious cases have changed over time. The epidemiological dynamics in Ecuador can range from 4 days to 14 days (interquartile range 2-7 days).[17-19] Among the main criteria are having returned from countries with active outbreaks 14 days prior to the onset of symptoms, being a health worker in units and settings that care for patients with acute respiratory failure of unknown etiology, or having a history of contact with positive cases of COVID-19.[17-19]

As for early-stage symptoms, the most common is fever (99 %; 88 % in hospitalized patients), followed by fatigue (70 %), dry cough (59 %), anorexia (40 %), myalgia (35 %), dyspnea (31 %), expectoration (27 %) and diarrhea (4 %).[9, 19-23]

In advanced stages, or as complications of evolution, pneumonia (being this the most frequent complication) and

bronchitis have been described. Irregular shadows and ground-glass radiopacity have also been reported in chest tomography images in patients with COVID-19.[9, 19-23]

The appearance of dyspnea has been reported after 8 days, as well as Acute Respiratory Distress Syndrome (ARDS), being frequent in patients with severe disease, also has been reported arrhythmias, acute heart failure and shock.[9, 19-23]

The mechanism of transmission is by droplets (greater than 5 microns) over a distance of 1 to 2.5 meters, after prolonged contact with people with symptoms or contaminated surfaces, hence it is more contagious in the symptomatic phase.The average age affected is between 30-50 years; 81% will have mild cases, rhinorrhoea is not common. 14 to 15 % will have pneumonia or severe cases requiring hospitalisation, and 5 % will have severe cases requiring hospitalisation in an intensive care unit. [19, 22-23]

Lethality ranges from 2 to 3%. It can increase to 14% in those over 80 years of age and mortality is close to 50% in severe cases .[22-23] Risk factors are advanced age, underlying respiratory disease, comorbidities, and immunosuppression.[19, 22-23]

Diagnóstico

Lymphopenia has been observed in 83% of cases, thrombocytopenia in 36% and can be accompanied by elevated CRP (C-reactive protein), transaminases, D-dimer[19-22]; however, for the diagnosis of the infectious agent the gold standard is the real-time polymerase chain reaction (RT-PCR), from respiratory samples.[10-16]

In case this methodology is not available, a chest CT can be used, since alterations have been reported in 86% of cases, with the ground-glass sign being

the most predominant. It can present in a single lobe or be multilobar, mono-lobar or bilateral in chest radiography should call attention infiltrated bilateral or lobar patch.[19-22]

Therapeutic recommendations

There is no specific antiviral treatment and treatments are conditioned. For this reason, many countries have implemented therapeutic indications based on clinical trials currently underway.

Within the clinical management of adults, the use of systemic steroids is not generally recommended, based on previous studies in patients with MERS, SARS and even influenza, from which it was demonstrated the non-benefit and even produced a delay in viral clearance.[24]

In cases of septic shock, vasopressors should be administered (MAP =/< to 65 mm/Hg), only if prolonged beyond 24 hours and, if associated adrenal insufficiency is considered, the use of hydrocortisone should be considered. Echocardiography is also recommended in the initial phase and in the follow-up of resuscitation. Dobutamine is advised in case of persistent shock or if myocardial dysfunction is proven.[24]

Antibiotics are not recommended initially, however, they may be added according to clinical evolution, analytical reports, or microbiological results, especially when other ethology or bacterial superinfection cannot be ruled out.[24]

One of the proposed drugs is lopinavir (protease inhibitor, used in the treatment of HIV) boosted with ritonavir, as it has been mentioned that it has activity against 3CL protease, with modest activity against SARS-CoV-2 20 based on its antiviral activity against MERS-CoV in vitro.[25]

Cao et al. conducted an open, randomized, controlled trial, which included hospitalized adult patients with confirmed SARS-CoV-2 infection. One group was assigned to receive lopinavir 400 mg / ritonavir 100 mg (LPV/r) scheme (n 99) versus a standard care (SCA) group. The research did not show a difference in the time to clinical improvement between the LPV/r group and EC (average of 16 days in both groups). They showed a shorter stay in the intensive care unit in the LPV/r group compared to EC (average 6 days vs. 11 days respectively), and from randomization to discharge (average 12 vs. 14 days). Mortality was numerically lower in the LPV/r group (19.2 %) than in EC (25.0 %). Clinical improvement was higher in the LPV/r group than in EC (45.5 % vs. 30.0 %). They concluded that LPV/r did not accelerate clinical improvement significantly, but it did reduce mortality and decreased detection of viral RNA in the patient with severe COVID-19.[26]

Remdesivir studies in the United States, South Korea and China have demonstrated efficacy in animal models for SARS-CoV and MERS-CoV.[16, 27, 28]

In Spain, therapeutic studies with lopinavir/r + IFN-β1b s.c, as well as lopinavir/r + IFN -α2b nebulized in a room with negative pressure, for the management of severe COVID-19. Chloroquine (CQ) and hydroxychloroquine (HCQ) have been mentioned as efficient in SARS-CoV-2 infection. The use of HCQ in SARS-COV-2 infection has been mentioned with a maximum dose in adults of up to 1,200 mg/day [CQ maximum dose 500 mg]. It has been stated that it "*exerts an antiviral effect during pre- and post-infection conditions by interfering with the glycosylation of angiotensin-converting enzyme 2 (ACE2) (the SARS-CoV cell receptor) and blocking the*

fusion of the virus with the host cell". This disruption of ACE2 terminal glycosylation can reduce the efficiency of binding between ACE2 in host cells and the SARS-CoV peak protein.[29]

Gautret et al. conducted a trial in patients from Marseille, who received hydroxychloroquine sulfate 200 mg 3 times a day for 10 days, while those who did not receive the HCQ served as a control group. The percentage of patients with negative PCR-RT results in nasopharyngeal samples differed from 3-4-5 and 6 days after inclusion; on the 6th day after inclusion, 70% of patients with hydroxychloroquine were virologically cured, compared to 12.5% of the control group.[30]

Tocilizumab has been mentioned as a therapeutic alternative in the management of COVID-19, according to experimental data. Based on proinflammatory cytokines released in the pathogenesis of SARS, which include interleukin (IL)-6, tumor necrosis factor α (TNF- α) and IL-12, as well as MERS in which elevated values of IL-6, IL- 1β and IL-8 were detected

.[19]

In a similar way, high values of IL-6, IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), interferon-inducing protein-γ (IP10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1 alpha (MIP1A), and TNF-α have been found in intensive care patients with VOC-19. Based on this information, Xu et al. conducted a study of 21 patients who were eligible for treatment with tocilizumab. The patients received a standard of care regimen with lopinavir, methylprednisolone, other symptomatic relief medications, and oxygen therapy, and tocilizumab 400 mg was added intravenously. They were able to show that body temperature returned to normal limits in all patients on day 1 of

tocilizumab and remained stable thereafter. It was accompanied by symptomatic synchronous relief in subsequent days. Patients significantly increased peripheral oxygen saturation, 75% of patients required less supplementary oxygen. One patient was taken off mechanical ventilation on day 1. Another critical patient was taken off ventilation and regained consciousness on day 5; improvement in lymphocyte and CRP levels was observed. 90.5% of the patients were discharged (including two critical patients), the rest remained in hospital, but without thermal rises and with notable improvement in symptoms, concluding that relief of symptoms, as well as a decrease in deterioration of patients with severe VOC-19 was evident in the group that received tocilizumab.[19, 31-34]

Within hospital management there is no proven evidence against the use of non-steroidal anti-inflammatory drugs (NSAIDs) in these patients, but paracetamol is always preferred.[22]

The use of antibiotics is not generally recommended in these cases, but if necessary, ceftriaxone or doxycycline are recommended instead of quinolones or macrolides, as the latter and some pharmacological agents used in antiviral treatment can prolong the QT wave.[22]

Azithromycin has been mentioned for showing in vitro activity against zika and ebola viruses, as well as in the prevention of severe infections of the respiratory tract; however, its use should be considered carefully in view of the risk of prolonging QT. Its use is recommended in combination with hydroxychloroquine, as it enhances the effect of this.[30]

Fluid therapy should be used only in patients with shock, systemic steroids should be avoided (with the exception of asthma as a background

comorbidity).[24] Pronation has been mentioned as a possible factor in improving the prognosis by not making it worse from a respiratory point of view.[24]

Favipiravir (FPV) is an antiviral medication that was subjected to an open control study as an experimental treatment for COVID-19, versus lopinavir/ritonavir (LPV/r) days 1-14, 400/100 mg twice a day) plus IFN-α by aerosol inhalation (5 million U twice a day), while FPV was administered on day 1 at doses of 1600 mg twice a day and from day 2-14 at doses of 600 mg twice a day, plus interferon (IFN) -α by aerosol inhalation (5 million U twice a day); the FPV arm showed significant improvement in chest imaging (91. 43 %) compared to the control group. Multivariate Cox regression showed faster viral clearance with FPV.[34]

A multicenter, open and randomized trial was also conducted [35] in which EC + PVF vs arbidol was compared, from February 20 to March 12, in patients with uncomplicated disease; a clinical recovery rate of 71.43 % with PVF and 55.86 % with arbidol was observed; a reduction in cough relief and fever reduction time was also evident, both among patients without comorbidities and in patients with hypertension or diabetes who received PVF.[35] Among the adverse effects, reactions of psychiatric symptoms, gastrointestinal symptoms and uric acid elevation were observed in 2.5% of cases. Therefore, Chen and collaborators (2020) propose it as a therapeutic alternative, based on the improvement observed after 7 days of treatment in uncomplicated patients.[36]

Infection prevention and control

Hand hygiene is the main method to avoid the transmission of the virus, both in the community and in the hospital environment, as well as the use of

surgical masks (based on the method of transmission), while FPP2 and FPP3 respirators are recommended in the case of procedures that generate aerosols.[19]

Among the key points recommended for prevention in the hospital environment are limiting the ways in which the virus can enter the facility and infect others (especially by cancelling elective procedures, enabling the use of telemedicine, limiting entry and exit points to healthcare facilities); Isolation precautions should be instituted for symptomatic patients as soon as possible in a ventilated area and separate triage should be performed (preferably by placing patients with suspected COVID-19 in rooms with closed doors and private bathrooms); Healthcare personnel should be protected by emphasizing hand hygiene, installing barriers to limit contact with triage patients, prioritizing the use of particle filtering respirators and isolation rooms for airborne pathogens.[36]

For those patients who require procedures that generate aerosols (since the most common route of dissemination is airborne, without ruling out hand contact with colonized surfaces or by the generation of aerosols). [36]

Healthcare personnel in contact with a confirmed or suspected case of VOC-19 should wear personal protective equipment (PPE) for contact, droplets and airborne pathogen transmission: fit-tested FFP2 or FFP3 respirator (N95), eye protection (i.e., goggles or face shield), long-sleeved gown and waterproof gloves.[38]

To optimize the use of PPE, especially in the case of shortages, it is acceptable for staff to use the same respirator while caring for several patients with the same diagnosis (without removing the

respirator, if the respirator is not damaged, dirty or contaminated), as this will moderate the consumption of PPE. The maximum time a respirator can be used is 4 hours, as long as it is not removed between patients or is contraindicated by the manufacturer.[39]

In case of shortage of hospital disinfectants, decontamination can be performed with 0.1% sodium hypochlorite (1:50 dilution when using household bleach at an initial concentration of 5%) after cleaning with a neutral detergent [38], although no data are available for the effectiveness of this approach against SARS-CoV-2; surfaces that may be damaged by sodium hypochlorite can be cleaned with a neutral detergent, followed by 70 % ethanol. [39-40].

Van Doremalen et al. analysed the stability of SARS-CoV-2 in aerosols and on surfaces, describing that in aerosols the virus remained viable for 3 hours (average 1.1 to 1.2 hours), in copper the viability was similar; the longest viability was in plastic (6.8 hours) and stainless steel (5.6 hours); thus they propose that the transmission of SARS-CoV-2 by aerosols and fomites is plausible, since it can remain viable for hours in aerosols and even days on surfaces.[41]

The use of facemasks and respirators is based on previous experience of the H1N1 pandemic, hence the recommendation that NIOSH-certified surgical masks and N95 respirators (which have a particle filtering capacity of 95%) and FFP2 (which have a filtering capacity of 92%) or FFP3 (which have a filtering capacity of 99%).[41-42]

The widespread use of N95 respirators has been strongly commented on in patients with pulmonary tuberculosis, especially because of the mechanism of transmission by aerosols, has

recommended them as an option for the optimization of PPE, in cases of epidemic outbreaks.[42, 43]

They should not be kept in pockets, plastic bags or confined areas. A maximum of 8 hours continuous use is recommended, or no more than 5 uses.[42] However, they should be discarded after use during aerosol generation procedures, or if they are contaminated with blood, respiratory secretions or other body fluids.[37, 38] It is not currently possible to specify a longer safe duration of use for the N-95 disposable respirator, but based on experience in industrial environments, 8 hours of continuous or intermittent use has been indicated as a safe duration.[37-40] Its prolonged use or reuse by the same user is recommended in scenarios such as the H1N1 influenza pandemic, as long as it retains its shape without alteration and its fixation on the face is adequate, always consulting experts in prevention and infection control.[32]

Respirators for use in the healthcare environment must always comply with NIOSH certification (http://www.cdc.gov/niosh/npptl/respirators/disp_part/particlist.html)[45], can be used in addition to the N series, the respirators R (relative resistance to oil particles) and P (strongly resistant to oil particles) 95, 99 and 100.[46] The use of valved respirators is recommended in the same patients that would wear a surgical mask (except for surgical procedures, or to prevent particles or infectious agents from spreading from health care personnel to the patient).[45, 46]

A standardized process involving rapid triage, isolation and movement of patients with suspected COVID-19 should be created to minimize the risk of transmission and exposure of healthcare personnel and other patients.[44, 46] Current recommendations

include a single room, negative pressure room with at least 6 air changes per hour.[18, 44-46]

The best strategy is prevention, avoiding touching the face with the hands, especially the T-zone (eyes, nose and mouth), frequent hand washing, more if it is health personnel, avoiding trips to areas with outbreaks or community distribution, and in health personnel the correct use of PPE.[46]

Strategies should be implemented to optimize the supply of N95 respirators, such as extended use or reuse up to 5 times.[46, 47]

Overalls or NBC suits?

No scientific evidence has been found to recommend the use of coveralls used in Ebola care. For the care of patients with COVID-19 [46-49]; PAHO/WHO recommends the use of disposable long-sleeved gowns to protect the clothing of health workers. In any case, the use of PPE, by health personnel, requires an assessment of the risk of transmission, as expressed previously.

Conclusions

SARS-CoV-2 is a betacoronavirus (zoonotic viral agent) whose origin is not clearly elucidated, and has been associated with a mutation from bat- or pangolin-preventing coronaviruses, which were transmitted to humans; its route of spread among humans is by droplets or aerosols (in healthcare facilities), as well as by mucous membrane contact with particles on surfaces through the hands.

Symptoms are varied, with fever and fatigue being the most common, and can be associated with myalgia and dyspnea (which can help us rule out diseases such as dengue, zika or chikunguya), diarrhoeal stools and other gastrointestinal symptoms. It should be noted that pneumonia is the most

common complication and that severe forms tend to be accompanied by ARDS.

There is not yet a therapeutic scheme of choice for this virus and many of those mentioned, of which good preliminary results have been mentioned, are still in the experimental phase, so their use should be handled with caution.

Hand hygiene and proper use of personal protective equipment should be emphasized. This use should always depend on the mechanism of transmission, in order to optimize the use of them, not to increase the costs of health care and to maintain an adequate supply for health workers, especially in countries with medium or low economies. Government authorities should establish flows and protocols that allow for the initiation of evidence-based treatment schemes.

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